UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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APR 25 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 8340-15: Review of rat teratology study with triphenyltin hydroxide submitted by the American Hoechst Corporation.

Tox Chem No. 896E

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Background:

The American Hoechst Corporation (Somerville, New Jersey) has submitted a rat teratology study in order to address questions regarding the possible teratogenic response of triphenyltin hydroxide as indicated in the Registration Standard for this chemical. In particular earlier studies with this chemical indicated that there were increased incidences of "hydronephrosis" and "hydroureter" and in another study the fetuses also developed "hydrocephalus". Refer to the Registration Standard dated March 27. 1984.

Toxicology Branch Response:

The study was reviewed and determined to be CORE GUIDELINES (see review attached).

Triphenyltin hydroxide was found to have a NOEL of >8.0 mg/kg/day (highest dose tested) for teratogenic effects. No evidence that the chemical resulted in teratogenic effects was presented.

There were some signs of possible fetotoxic effects (delayed ossification) at the highest dose level tested (NOEL = 2.8 mg/ kg/day).

The NOEL for maternal toxicity was 1.0 mg/kg/day. At 2.8 mg/kg/day there was evidence of body weight loss and at 8.0 mg/kg/day there was both weight loss lesser food consumption and poor overall condition of the dams as well as one compound related abortion and increased numbers of resorptions and lower pup weight at delivery.

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STUDY TYPE: Teratology-rat: [A teratology study in rats with triphenyltin hydroxide (Code HOE 029664 OF ZD97 0001 Technical Substance]

Accession No: 257402

MRID No.

Sponsor: American Hoechst Corporation, Somerville, New Jersey

Contracting Lab: Wil Research Laboratories, Ashland, Ohio (Study No. Wil 39011)

Date: April 1, 1985

Test material: Triphenyltin hydroxide (TPTH) was provided by Hoechst AG, Germany. The sample had the code number HOE 029664 OF ZD97 0001 and was stated as being certified to be 97.1% pure.

Review of Study

Study Protocol (basic design): 5 groups of 45 mated female Sprague-Dawley rats (Crl, CD®(SD) BR) obtained from the Charles River Breeding Laboratories, Portage, Michigan were dosed with either 0.00, 0.35, 1.00, 2.80 or 8.00 mg/kg of test material dissolved in corn oil on days 6-15 of gestation (10 doses). The dosage was adjusted so that each rat was dosed with 5 ml/kg of corn oil by gavage. Although each group consised of 45 females there were actually 41, 39, 41, 39 and 36 gravid females for the dose groups respectively. The rats were sacrificed on the 20th day of gestation by carbon dioxide asphyxiation and their pups delivered by Cesarian secton.

Maternal Effects: The testor asserts a NOEL for maternal effects of 1.0 mg/kg. None of the rats died. Single rats in groups receiving 1.0 and 8.0 mg/kg aborted or delivered prematurely. The abortion in the high dose group but not the early delivery in the mid low dose group were attributable to the test material. The rat which had an early delivery on day 16 in the lower mid dose group produced normal appearing pups and the early delivery was attributed to an error in noting the exact time of copulation.

There were 41, 39, 40, 38, and 31 dams per dose group respectively which had viable fetuses delivered by Cesarian section. Resorptions of the whole litters were noted only in the high intermediate (2.8 mg/kg) and high dose groups. There were 4 dams which had litter resorptions in the high dose group and a single dam in the other group. The dam in the high mid dose group also developed complications due to intubation injury which were considered to have resulted in the litter resorption. The mean number of early resorption sites was statistically significantly higher for the low and the high dose test groups. Only the high dose test group increase was considered to be biologically meaningful.

Statistically significant body weight decreases were noted for the high dose groups (6-12%) starting at day 9 and until sacrifice. There was an initial decrease in bodyweight gain for the high mid dose group on days 6-9 of gestation, but this group was similar to controls at later intervals. Food consumption was decreased 10-22% for the high mid dose group and up to 50% for the high dose group. The low and low mid dose groups were reported to have body weight gain and food consumption data similar to the controls.

Other indications of toxicity responses in the treated dams included: "emaciated", "lethargic", hair loss, yellow anogenital staining, red vaginal discharge, and dried red matting in the anogenital area. Some of the effects such as increased hair loss were also noted in the 1.0 mg/kg dose group, but because of the subjective nature of this observation, TB concurs with the test report that the NOEL is 1.0 mg/kg/day for maternal toxicity. At 2.8 mg/kg there were signs of weight loss and decreased food consumption of a mild degree. TB does not concur with the testor in the description of the symptoms being severe at the highest dose level.

Uterine Data:

There were 570, 549 (-4%), 557 (-2%), 514 (-10%) and 399 (-30%) viable pups in the control, low, mid low, mid high and high dose test groups. There were no dead fetuses reported but there was a statistically significant increase in early resorptions and implantation loss for the high dose group. Mean fetal weight for the high dose group was 11% lower than for the control but the average pup weight for the high mid dose group was comparable to the controls. There were no differences in the mean implantation sites or mean number of corpora lutea.

A NOEL of 2.8 mg/kg/day is supported. At 2.8 and 8.0 mg/kg there were fewer pups but at the 2.8 mg/kg dose level there was no correlative toxicity signs with the lower percentage of viable births (10%). Thus the 10% decrease is not definitely related to the test material and dose not reach statistical significance as assessed by the testor using Dunnett's test.

Pup Data:

The testor asserts a NOEL for fetotoxic effects of 2.8 mg/kg and that there are no teratogenic effects due to the test material.

1. External observation (all pups were said to have been examined): There were 12 fetuses from 12 different litters with malformations noted. No one lesion type had more than 2 incidences reported. There were, however, 6 pups affected in the high dose group and only 1 or 2 pups affected in the other test groups. When expressed as a percentage, the high dose group has 1.5% versus 0.4% malformations for the other test groups. The small magnitude of this increase together with the large number of pups available for assessment precludes a definite test chemical effect for development of external malformations. Thus, the NOEL for externally visible malformations is >8.0 mg/kg/day.

2. Visceral examination: 285, 275, 278, 257 and 201 fetuses for the control to the high dose groups respectively were fixed in Bouin's fixative and examined for soft tissue abnormalities using the sectioning technique of Wilson.

There were four different types of visceral abnormalities reported. There were single incidences (only one pup affected with each lesion) of "testicular agenesis" and "major blood vessel variation" reported. There were four pups representing four different litters affected with "hydrocephaly". When expressed as a percentage of the pups available per group there were 0.4, 0.0, 0.0, 0.4, and 1.0% of the pups affected. There were 2.4, 0.0, 0.0, 2.6 and 6.7% of the litters affected. A tendency toward a dose related increase is noted but the small magnitude of the increase prevents a conclusion of a definite test chemical effect. It should be noted that TPTH resulted in increased incidences of hydrocephalus in the Sprague-Dawley rat in an earlier study (refer to p 39 of the TB chapter of the TPTH registration standard) but the magnitude of the increase was far more evident and statistical significance was attained in the earlier study.

There were no lesions described as "hydroureter" or "hydronephrosis" reported. Rather there were lesions in the kidney described as "renal papilla(e) not developed and/or distended ureters". The following table illustrates the response:

Dose Level (mg/kg)	n	Pups With kidney/ureter lesions	n	Litters With pups with kidney/ ureter lesion
0.00	285	20(7.0)/21(7.4)*	41	14(34.1)/15(36.6)
0.35	275	20(7.3)/21(7.6)	39	14(35.9)/15(38.5)
1.00	278	10(3.6)/11(4.0)	40	7(17.5)/8(20.0)
2.80	257	20(7.8)	38	12(31.6)
8.00	201	14(7.0)	30	10(33.3)

n=the number of pups or litters available for examination.

*The numerator indicates the tabulation as reported by the testor with the percentage in (). The denominator represents the tabulation by TB where a difference was found.

The historical control data provided indicated that in this strain of rat up to 7.5% of the rat pups and up to 32% of the litters spontaneously develop the renal lesion described above.

Thus, there was no evidence that TPTH dosing resulted in increased incidences of either renal, bladder, or urinary tract lesions in this study. The data presented support a NOEL of >8.0 mg/kg/day for visceral effects in the fetuses.

3. Skeletal examination: The fetuses not prepared for visceral examination were prepared for skeletal examination following evisceration, fixing in 95% isopropyl alcohol, maceration in KOH and staining with Alizarin Red S and later examination under low power microscopy.

The were 13 types of skeletal anormalities reported. Of these only a lesion described as "sternebra(e) #5 and/or #6 unossified" showed a statistically significant increase in the high dose test group. The response for this lesion type is illustrated in the table below:

Dose Level (mg/kg)	n	Pups Affected	n	Litters Affected
0.00	285	36	40	16
0.35	274	41	39	17
1.00	279	27	40	17
2.80	257	17	38	13
8.00	198	41	31	21*

*Statistically significant, P at 0.05 (Fishers Exact Test)

The testing laboratory asserts that the increase in unossified skeletal

development is a result of the maternal toxicity of TPTH and is not a specific effect of TPTH on the fetus. TB concurs with this interpretion. It should also be noted that the spontaneous occurrence of "sternebra(e) #5 and/or #6 unossified" is from 4.6 to 36.6% of the pups and from 25.0 to 100% of the litters according to historical control data provided for this strain of rat.

CORE Classification. This study is Core Guidelines. The study data support a NOEL for maternal toxicity of 1.00 mg/kg/day. At higher levels (2.8 and 8.00 mg/kg/day) there are "general" signs of toxicity including weight loss and poor overall condition of the rat and the pup weight was decreased and there were fewer fetuses for the high dose test group. A NOEL for fetotoxic effects of 2.8 mg/kg is supported. At the next higher level (8.0 mg/kg) there is experimental evidence of unossified sternebra(e) which is unlikely a specific effect of TPTH. There was no evidence of a specific teratogenic effect of TPTH presented in this study up to and including 8.0 mg/kg/day.

Important aspects of this study which greatly affects its acceptability and demonstration for a lack of teratogenic effects (especially related to the kidney/bladder/urinary tract system) is that each dosage group contained 31-41 dams which had pups for delivery instead of the recommended lower limit of at least 20. Thus there were from 1.55 to 2 times as many fetuses available for examination as would be recommended. The study also presented historical control data for the spontaneous occurrence of various lesions in this strain of rat from a total of 713 rats of which 644 had litters. There were reported a total of 8965 pups given visual examination and 5440 pups given visceral examination and 5931 pups examined for skeletal effects.